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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,075	12/17/2003	Perry F. Renshaw	04843/117002	1400

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EXAMINER	
FEDOWITZ, MATTHEW L	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/740,075	RENSHAW ET AL.	
	Examiner	Art Unit	
	Matthew L. Fedowitz	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☒ Claim(s) 8 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending in this action.

Claim Objections

Claim 8 is objected to because the claim should use the term "administration" instead of "administering." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 12, 15 and 17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is directed to normalizing the sleep/wake cycle of a mammal; however, the meaning of the term "normalizing" is unclear in light of the specification. The specification only states "a normal sleep/wake cycle involves sleeping at night and being awake during the day, although other sleep/wake cycles are possible, e.g., sleeping during the day and working at night." The specification states two different alternatives to sleeping where the first is being awake and the other is working. This raises the question as to whether the terms awake and working are synonymous. Often times it is not necessary to be awake to be working. For example, many times physicians, while working, take naps while performing shift work. Taking

a nap is universally considered to be sleeping and therefore the example shows how one may be working and sleeping or not awake at the same time.

Claim 2 further narrows claim 1 and contains the terms fatigue, tiredness and sleep quality. Fatigue and tiredness are not defined in the specification and as a result it is unclear what is meant by these terms. For example, fatigue and tiredness may refer to metal fatigue or tiredness or even physical fatigue or tiredness where there can be a combination of both or even neither when some other meaning can be contrived. The term sleep quality is unclear because, in considering its meaning in light of the specification, the definition provided is that of a measure of actual rest obtained from sleep, as opposed to the length of time that a mammal is asleep. This is indefinite because the terms "actual rest" is unclear. Does "actual rest" refer to sleep that contains the rapid eye movement stage (REM) and non-rapid eye movement stage (NREM) or neither (see Shargel *et al.* pp. 547-548)?

Claims 1 and 12 are directed to the use of a "therapeutically-effective amount" of the claimed compound. The specification defines this term as that which is sufficient to produce a healing, curative, prophylactic, stabilizing, ameliorative effect in a mammal suffering from a sleep disorder. The specification provides no references points from which to measure a therapeutically effective amount and is therefore indefinite.

Claim 15 narrows claim 12 and is directed to defining the sleep disorders. The phrase "problem sleepiness" is not defined in the specification and is unclear as to its meaning. Problem sleepiness can be construed to mean a condition that makes one too sleepy or a condition where one is not sleepy enough.

Claim 17 is directed to a method of increasing cognitive function. The term cognitive function is not defined within the specification and could be construed to mean one's memory, thinking ability or even brain wave activity. As a result, the phrase "cognitive function" is indefinite.

Claims 2-11, 13-14, and 18 are indefinite as well because claims that depend from an indefinite claim are also indefinite. Ex parte Cordova, 10 USPQ2d 1949 (Pt. Bd. App. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwell in view of Weiss, Renshaw *et al.* (US 5,958,896) and Katzung.

Claim 1 is directed to a method of normalizing the sleep wake by administering a therapeutically effective amount of a cytidine-, cytosine-, uridine-, creatine-, adenosine-

containing compound and an adenosine elevating compound to a mammal to normalize the sleep/wake cycle. Claim 2 narrows claim 1 to where claim the administration reduces fatigue, tiredness, increases wakefulness, or improves sleep quality. Claim 3 narrows claim 1 to cytidine-containing compounds to cytidine. Claim 4 narrows claim 1 to where the cytidine-containing compound is choline. Claim 5 narrows claim 1 to where the cytidine containing compound is CDP-choline. Claim 6 narrows claim 5 to oral administration of CDP-choline. Claim 7 narrows claim 1 to where the compound is CDP. Claim 8 narrows claim1 to a chronic administration profile. Claim 9 narrows claim 1 to mammals. Claim 10 narrows claim 9 to children or adolescents. Claim 11 narrows claim 9 to older adults. Claim 12 is directed to a method of treating a sleep disorder by administering a therapeutically effective amount of a cytidine-, cytosine-, uridine-, creatine-, adenosine-containing compound and an adenosine elevating compound. Claim 13 narrows claim 12 to sleep disorder caused by a substance abuse disorder. Claim 14 narrows claim 13 to substance abuse disorders such as alcohol, caffeine, or cocaine usage or dependence. Claim 15 narrows claim 12 to sleep disorders such as insomnia, constructive or obstructive sleep apnea, restless leg syndrome, periodic limb movements, problem sleepiness or narcolepsy. Claim 16 narrows claim 12 to the cytidine containing compound being CDP-choline. Claim 17 is directed to a method of increasing cognitive function by administering a therapeutically effective amount of a cytidine-, cytosine-, uridine-, creatine-, adenosine-containing compound and an adenosine elevating compound. Claim 18 narrows claim 17 to the cytidine containing compound being CDP-choline.

In light of the 35 U.S.C. § 112 second paragraph rejection above, claims 1, 2, 12, 15 and 17 will be construed in the following manner. The term "normalizing" in claim 1 will be

construed to mean maintaining. The term therapeutically effective in claims 1 and 12 will be construed to mean any amount that maintains sleep. In regard to claim 2, the terms fatigue and tiredness will be construed to mean the state of falling asleep and sleep quality will be construed to mean sleep that is not light sleep. In regard to claim 15, the terms problem sleepiness will be construed to mean light sleep. Cognitive functioning in claim 17 will be construed to mean any function that the brain may be involved with.

Greenwell teaches that choline is needed for brain function and that choline is required for the synthesis of acetylcholine; that acetylcholine is vital for thought, memory and sleep; that acetylcholine is helpful in maintaining sleep by controlling sensory input, decreasing the chance of becoming a light sleeper; that choline supplementation results in enhanced cognitive function and performance; that 1-3 grams daily is sufficient for the elderly and that 250mg daily may be sufficient for a younger person where daily is construed to mean chronic use (see paragraphs 1-10).

Greenwell does not teach the metabolism of CDP-choline that results in CDP and choline acting as components in the synthesis of acetylcholine; that cytidine is one of the components of CDP-choline or the use of CDP-choline treatment of sleep disorders associated with substance abuse disorders such as alcohol, caffeine or cocaine usage.

As relating to claims 1, 3-5, 7, 12, 16 and 18 and the claims depending therefrom, Weiss teaches the metabolism of CDP-choline and that CDP-choline metabolism results in products for the formation of acetylcholine. Weiss also teaches that cytidine is one of the components of CDP-choline (see figure 3 on p 641).

In reference to claims 12-14, Renshaw et al. teach the use of CDP-choline for the treatment of stimulant exposure and the dependence thereupon; the use of cytidine, cytosine, choline and CDP in humans as well as a therapeutically effective amount of the cytidine containing compound (see claims 1-27).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to create compounds for the normalization of the sleep/wake cycle having the above cited references before him. By considering all the prior art cited, it would lead one skilled in the art to have a reasonable expectation of success in combining Greenwell with Weiss and Renshaw *et al.* to produce the methods claimed.

Greenwell and Katzung provide the motivation for this method of using compounds for the normalization of the sleep wake cycle. Greenwell specifically states that one of the lesser-known functions of choline is to maintain sleep. And Katzung teaches that one of the effects of withdrawal of stimulant use is that users deprived of the drug become sleepy (see page 522); moreover, it is a natural step to look for a treatment to this sequelae of the stimulant use in treating the disease so that it is only a therapeutic exercise (see p. 62).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Matthew L. Fedowitz whose telephone number is (571) 272-3105 and can be reached between 9am-5:30pm (EST) M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Mr. James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew L. Fedowitz, Pharm.D., J.D.
December 6, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623